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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/623,458	07/17/2003	**Baback Gharizadeh**	87835.2	3111

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EXAMINER	
BABIC, CHRISTOPHER M	
ART UNIT	PAPER NUMBER
1637	

MAIL DATE	DELIVERY MODE
12/26/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/623,458	GHARIZADEH, BABACK	
	Examiner	Art Unit	
	CHRISTOPHER M. BABIC	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 September 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-12 and 17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 3-12, and 17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

Claim(s) 1, 3-12, and 17 are pending. The following Office Action is in response to Applicant's communication dated September 25, 2008.

Claim Rejections - 35 USC § 103 - Maintained

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

1. Claim(s) 1, 3-6, and 17 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Alderborn et al. ("Determination of single-nucleotide polymorphisms by real-time pyrophosphate DNA sequencing." Genome Res. 2000 Aug;10(8):1249-58) in view of Ronaghi ("Improved performance of pyrosequencing using single-stranded DNA-binding protein." Anal Biochem. 2000 Nov 15;286(2):282-8), and in further view of Caskey et al. (U.S. 5,582,989).

With regard to claim 1, Alderborn teaches a determination of single-nucleotide polymorphisms (SNPs) by real-time pyrophosphate DNA sequencing (fig. 1; abstract,

for example). Specifically, Alderborn teaches the providing of a sample containing target DNA with variable sequence regions (fig. 2-4; pg. 1257, DNA amplification, for example); providing sequencing primers and allowing such primers to hybridize to such DNA target (fig. 2-4; pg. 1257, annealing to identification oligonucleotide, for example); and sequencing such variable regions through pryosequencing (fig. 2-4; pg. 1257, solid-phase pyrosequencing, for example).

Alderborn does not expressly teach providing a mixed pool of structurally different primers, each primer being specific for one species, group, or target, and mixing such mixed pool of primers with a target DNA; however, Alderborn expressly teaches identification of multiple different SNP sites on a single target DNA utilizing one primer (pg. 1253, teaches the primer elongation reaction proceeding over 18 bases of a template to elucidate two SNPs located 15 bases apart, for example). Thus, it was clear in the art at the time of invention that multiple SNP sites could be resolved in one reaction.

With regard to claim 17, Alderborn teaches pattern recognition (fig. 2-4, for example).

With regard to the use of two structurally different primer to resolve multiple SNP sites, it is first submitted that, as highlighted by Applicant on page 10 of Applicant's disclosure, at the time of invention the prior art recognized that pyrosequencing technology was limited to sequencing only short to medium sequence lengths, i.e. read length. Ronaghi provides a supportive disclosure that highlights the limited read length ability of the pyrosequencing method, even in the presence of a single stranded binding

(SSB) protein, i.e. Ronaghi teaches that even after the addition of SSB, the pyrosequencing method only provides a read length of about 30 nucleotides (abstract; fig. 2, for example). Thus, it was clear in the art at the time of invention that the pyrosequencing method was limited to shorter sequence lengths.

In addition, the extension of multiple primers, each primer drawn to different target sequences, within the same reaction was a well known concept at the time of invention, i.e. multiplex extension. In particular, Caskey highlights the advantages of multiplexing nucleic acid amplification utilzing multiple structurally different primers, including the ability to detect multiple different separated target sequences, as well as the ability to detect multiple different loci of the same target sequence separated by large sequences in between the loci (col. 7, lines 20-55, for example).

With regard to claims 3 and 4, Caskey teaches multiple different target DNA from virus and bacteria (col. 5, lines 45-60, for example).

With regard to claims 5 and 6, Caskey teaches multiple different disease-linked variants (col. 7, lines 20-55, for example).

Thus, it was clear in the art at the time of invention that multiple different target sequences could be extended in a polymerase extension reaction.

In summary, it was clear in the art at the time of invention that the one primer within a pyrosequencing reaction would be unable to elucidate multiple SNP sites separated by large sequences (e.g. hundreds-thousands of nucleotides).

Thus, in summary, it is submitted that it would have been *prima facie* obvious to a skilled artisan at the time of invention to utilize multiple structurally different primers

within the same reaction for detection of multiple different SNP sites separated by large sequences, i.e. multiplex SNP detection, since the prior art demonstrates that such primers can extend different target loci separated by large sequences. A skilled artisan would have had a reasonable expectation of success with such a method since the prior art demonstrates that pyrosequencing can identify multiple different SNP sites within the same reaction.

Response to Arguments

Applicant's arguments have been fully considered but they are not persuasive.

With regard to Applicant's arguments regarding evidence of long-felt need, there is no evidence that if persons skilled in the art who were presumably working on the problem knew of the teachings of the above cited references; they would still be unable to solve the problem. See MPEP § 716.04. For example, the most relevant reference provided by Applicant, Gharizadeh (remarks, pg. 3), recites that, "At present, pyrosequencing might not be particularly useful for identifying infection with more than one HPV genotype because multiple infections give sequence signals from all of the available types on the specimen." It is submitted that such evidence when taken together with the cited observations of Alderborn, who proves that multiple nucleotide positions could be elucidated by pyrosequencing within a single reaction, would have led a skilled artisan to a reasonable expectation of success when using pyrosequencing to elucidate multiple genotypes within a single reaction.

In response to applicant's argument that Alderborn is nonanalogous art, it has been held that a prior art reference must either be in the field of applicant's endeavor or, if not, then be reasonably pertinent to the particular problem with which the applicant was concerned, in order to be relied upon as a basis for rejection of the claimed invention. See *In re Oetiker*, 977 F.2d 1443, 24 USPQ2d 1443 (Fed. Cir. 1992). In this case, it is first noted that the claimed invention is not exclusively limited to identification of multiple infections within an individual. The claimed invention encompasses elucidating two nucleotide positions on a single target nucleic acid, as disclosed within Aderborn. Furthermore, even if the claimed invention did exclusively require two different target pathenogenic nucleic acids (e.g. multiple HPVs) for detection, the teachings o Alderborn are reasonable pertinent to the particular problem of nucleic acid detection.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Thus, the rejection is maintained.

2. Claim(s) 7-12 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Alderborn et al. ("Determination of single-nucleotide polymorphisms by real-time pyrophosphate DNA sequencing." Genome Res.

2000 Aug;10(8):1249-58) in view of Ronaghi ("Improved performance of pyrosequencing using single-stranded DNA-binding protein." Anal Biochem. 2000 Nov 15;286(2):282-8), and in further view of Caskey et al. (U.S. 5,582,989) as applied to claim 6 above, and in further view of Rady et al. ("Type-specific primer-mediated direct sequencing of consensus primer-generated PCR amplicons of human papillomaviruses: a new approach for the simultaneous detection of multiple viral type infections. J Virol Methods. 1995 Jun;53(2-3):245-54").

The methods of the previously applied reference(s) have been outlined in the above rejections. The previously applied reference(s) do not expressly teach sequencing of HPV.

With regard to claim(s) 7-10, Rady provides a supporting disclosure that teaches the amplification of a conserved region within multiple different HPV types and subsequent sequencing with sequence specific primers (page 246-249, materials and methods; fig. 1, for example).

With regard to claim(s) 11, the sequencing of low yield amplification of fragments is inherent to the methods of Ye.

Thus, in summary, it is submitted that it would have been *prima facie* obvious to a skilled artisan at the time of invention to utilize the methods suggested by the prior applied references to detect certain HPV types within a sample since the prior art demonstrates such methods as capable of identifying many different nucleic acid

templates within the same reaction, thereby reducing the time needed for many separate reactions.

With regard to claim(s) 12, Caskey teaches the importance of designing primers that do not anneal to unspecific sequences (col. 4, lines 25-55, for example). Thus, it would have been *prima facie* obvious to a skilled artisan at the time of invention to design the multiplex sequencing primers such that they do not anneal to unspecific sequences and provide erroneous sequencing information.

Response to Arguments

Applicant's arguments have been addressed in the response(s) set forth above.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any

extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher M. Babic whose telephone number is 571-272-8507. The examiner can normally be reached on Monday-Friday 7:00AM to 4:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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